term "biological characteristic" as added in new independent claims 22 and 28 is found in the specification on page 14, lines 13-20 and in the claims as filed. No new matter has been added by these new claims. Therefore, claims 1-30 are pending and at issue.

The amendments to the specification were made to correct typographical errors in authors' names, incorrect page numbers for citation of references, and inconsistent punctuation for citations. No new matter has been added by these amendments.

Reconsideration of the above identified application, in view of the above amendments and the following remarks is respectfully requested.

Information Disclosure Statement

Responsive to the Examiner's request in item 3 on page 2 of the Office Action, the missing references will be hand-delivered to the PTO under separate cover.

Rejections Under 35 U.S.C. §112

The Examiner has rejected claims 1-9, 16, 18 and 20 for allegedly lacking adequate enablement. The Examiner contends that the specification only provides enablement for a method of treating prostate cancer in mammals by administering the anti-HER2 antibody 2C4, and does not reasonably provide enablement for a method of treating a human having prostate cancer or androgen dependent prostate cancer wherein the method comprises administering any anti-ErbB2 antibody.

Cancellation of claims 16, 18, and 20 moots this rejection in part. With respect to claims 1-9, however, Applicants respectfully traverse this rejection, and reconsideration is respectfully requested.

Claim 1, and claims dependent thereon, is directed to a method of treating prostate cancer by administering an antibody that binds ErbB2 and blocks ligand activation of an ErbB2 receptor. As the Examiner recognizes (this is clear from the references cited in rejecting the claims as anticipated or obvious), antibodies that bind ErbB2 are known. There can be no question as to enablement of such antibodies. Furthermore, given the well-developed antibody art, which has led to routine production and screening of antibodies against well-characterized antigens, there is no question as to enablement of an antibody that, in addition to binding an ErbB2 receptor, also blocks ligand activation of an ErbB2 receptor, as the specification describes (page 13, line 37 to page 14, line12):

> An antibody which "blocks" ligand activation of an ErbB receptor is one which reduces or prevents such activation as hereinabove defined, wherein the antibody is able to block ligand activation of the ErbB receptor substantially more effectively than monoclonal antibody 4D5, *e.g.* about as effectively as monoclonal antibodies 7F3 or 2C4 or Fab fragments thereof and preferably about as effectively as monoclonal antibody 2C4 or a Fab fragment thereof. For example, the antibody that blocks ligand activation of an ErbB receptor may be one which is about 50-100% more effective than 4D5 at blocking formation of an ErbB hereto-oligomer. Blocking of ligand activation of an ErbB receptor can occur by any means, *e.g.* by interfering with: ligand binding to an ErbB receptor, ErbB complex formation, tyrosine kinase activity of an ErbB receptor in an ErbB complex and/or phosphorylation of tyrosine kinase residue(s) in or by an ErbB receptor. Examples of antibodies which block ligand activation of an ErbB receptor include monoclonal antibodies 2C4 and 7F3 (which block HRG activation of ErbB2/ErbB3 and ErbB2/ErbB4 hereto-oligomers; and EGF, TGF-∝, amphiregulin, HB-EGF and/or epiregulin activation of an EGFR/ErbB2 hereto-oligomer); and L26, L96 and L288 antibodies (Klapper *et al. Oncogene* 14:2099-2109 (1997)), which block EGF and NDF binding to T47D cells which express EGFR, ErbB2, ErbB3 and ErbB4.

The specification exemplifies these assays, further establishing enablement of this aspect of the claimed invention. For example, Example 2 describes an assay for antibody-medicated inhibition of association of ErbB2 with ErbB3 (specification at page 45, line 24 to page 46, line 18),

and Example 4 describes antibody inhibition of EGF-, TGF-∝, and HRG-medicated activation of MAPK (specification at page 50, lines 8-26). See also page 32-34 of the specification.

Finally, anti-ErbB2 antibodies, such as HERCEPTIN®, are known to be useful for treating cancers. Again, the Examiner has acknowledged this in the prior art cited. However, prior to the present invention, there was no disclosure in the art of the characteristics of anti-ErbB2 antibodies that would prove therapeutically effective against prostate cancer, particularly androgen independent prostate cancer.

Applicants have unexpectedly discovered that an antibody that binds ErB2 and blocks ligand activation of an ErbB receptor, such as ligand-mediated activation of tyrosine kinase or ErbB2 heter-oligomer formation or heregulin-mediated activation, to a greater extent than monoclonal antibody 4D5 (which also binds ErbB2), inhibits prostate cancer tissue growth to a greater extent than Herceptin®. These findings characterize the desired properties of the presently claimed antibody and which will enable others to generate comparable antibodies effective for treating prostate cancer. The Examiner has acknowledged that "inventors should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings." Given the highly developed state of the art, which enables anti-ErbB2 antibodies and determining the characteristics of such antibodies without undue experimentation, in combination with the disclosure of which such antibodies are effective for therapy of prostate cancer, there is no reasonable basis to doubt enablement of the claimed invention.

The Examiner has rejected claims 2, 4-5, and 20 as allegedly lacking adequate enablement. The Examiner contends that the claims contain subject matter which was not set forth

in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. However the Examiner provides that a declaration accompanying the deposit of biological materials would overcome this rejection.

In response, a copy of such a declaration is provided herewith. The specification references the deposit of four hybridoma cell lines which produce monoclonal antibodies 7C2, 7F3, 4D5 and 2C4, respectively, on page 42, lines 29-36. Reconsideration and withdrawal of the rejection is respectfully requested in view of submission of the enclosed declaration.

Rejections Under 35 U.S.C. §102

The Examiner has rejected claims 1 and 8 under 35 U.S.C. §102(e). The Examiner contends that the rejected claims are anticipated by Greene et al., U.S. Patent 5,842,311 ("Greene"), published October 20, 1998, or Arakawa et al., U.S. Patent 5,783,186 ("Arakawa"), published July 21, 1998. The Examiner has further rejected claims 1, 8, and 16 over these two references as evidenced by Murphy et al., The American Society Textbook of Clinical Oncology, 1995, pages 126-127. Because Murphy adds nothing to Greene or Arakawa with respect to claims 1 and 8, and claim 16 has been cancelled, these rejections are addressed together.

The Examiner contends that Greene teaches a method of treating the activated p185 oncogene, found in prostate adenocarcinoma, by administration of an antibody. The Examiner contends that Arakawa teaches a method of treating a patient by using monoclonal antibodies which bind to ErbB2 to treat mammalian cancer tumors which express HER2 on their surface.

Applicants respectfully traverse this rejection and reconsideration is respectfully

requested.

Claim 1 recites that the antibody blocks ligand activation of an ErbB receptor. We can look to the specification to define the meaning of this term. The specification states that an "antibody which 'blocks' ligand activation of an ErbB receptor is one which reduces or prevents such activation as hereinabove defined, wherein the antibody is able to block ligand activation of the ErbB receptor substantially more effectively than monoclonal antibody 4D5, *e.g.* about as effectively as monoclonal antibodies 7F3 or 2C4 or Fab fragments thereof and preferably about as effectively as monoclonal antibody 2C4 or a Fab fragment thereof." (Specification, page 13, line 37 to page 14, line 4). The antibodies disclosed in Greene do not block ligand activation and certainly not to a greater extent than 4D5. Greene discloses that the cytotoxic mechanism of the cytotoxic effect is unknown, but that it is likely due to antibody-mediated cellular cytotoxicity, as evidenced by experimental results Greene (col. 30, lines 30-35). Similarly, Arakawa merely discloses that the monoclonal antibody described therein induces apoptosis through a phosphorylation-dependent mechanism (col. 3, lines 1-6). There is no disclosure in Arakawa that the monoclonal antibody blocks ligand activation of cells in the manner required by the teachings of the instant invention. Therefore, the invention is not anticipated by either Greene or Arakawa because the claims require the therapeutic antibody block the ErbB receptor more effectively than previously known therapeutic anti-ErbB monoclonal antibodies, *i.e.*, Herceptin®.

The Examiner has rejected claims 1, 6, 8-9, and 16 under 35 U.S.C. §102(b). The Examiner contends that rejected claims 1, 6, and 8-9 are anticipated by Curnow, Cancer Immunology

Immunotherapy, Vol. 45., pages 210-215, 1997 alone, and these claims plus claim 16 by Curnow as evidenced by Murphy et al., The American Society Textbook of Clinical Oncology, 1995, pages 126-127. Since Murphy adds nothing to Curnow with respect to claims 1 and 8, and claim 16 has been cancelled, the rejections are considered together. The Examiner contends that Curnow teaches a method of treating a human patient by administering an antibody which binds ErbB2 and blocks activation of an ErbB receptor.

Applicants respectfully traverse this rejection and reconsideration is respectfully requested.

Curnow discloses a bispecific antibody, that binds CD64 antigen and HER2/neu, designated MDX-H210. Such an antibody brings a CD64-positive effect cell in proximity of a HER2/neu bearing cell. Curnow does not disclose or even suggest that MDX-H210 blocks ligand activation of an ErbB2 receptor. To the contrary, Curnow proposes that MDX-H210 (non-humanized anti-HER2/neu) directs phagocytosis of tumor cells by antigen presenting cells, resulting in the presentation of tumor antigens and induction of a humoral response, and that this same activity has been suggested for MDX-H210. Thus, Curnow does not teach an antibody that blocks ligand activation of an ErbB receptor for treating prostate cancer; the reference teaches quite the opposite, in fact. In view of the preceding, and the legal test described above, Curnow cannot anticipate the claims of the instant application. Withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. §103

The Examiner has rejected claims 1, 8, and 16 under 35 U.S.C. §103(a). The Examiner contends that claims 1 and 8 are unpatentable over Hudziak et al., U.S. Patent

5,725,826 ("Hudziak"), issued March 10, 1998 in view of Ching (the full name of the author is Karen Zhi Ching), Dissertation Abstracts, Vol. 55, No. 11, page 4738-B, May 1995 ("Ching"). The Examiner further contends that claims 1, 8, and 16 are obvious over these two references as evidenced by Murphy. Murphy adds nothing to the rejection of claims 1 and 8, and claim 16 has been cancelled. Because resolution of these rejections concerns the same issue, they are addressed together.

The Examiner contends that Hudziak teaches that the HER2 oncogene has been found active in numerous cancers, and further provides a method of using monoclonal antibodies which bind to ErbB2 to treat mammalian cancer tumors which express HER2 on their surfaces (Office Action, p. 13). The Examiner contends that Ching teaches that prostate cancer overexpresses HER2. The Examiner further contends that Murphy teaches that the term "prostate cancer" generally refers to androgen dependent prostate cancer.

Applicants respectfully traverse this rejection and reconsideration is respectfully requested.

The preferred monoclonal antibody 4D5 in Hudziak inhibits the growth of breast tumor line SKBR3 (col. 18, lines 13-18). However, the present invention is directed to use of antibodies that block ligand activation of an ErbB receptor to a greater degree than 4D5. Hudziak does not specifically mention the desirability of this property for treating prostate cancer. Ching does not supply the missing teaching.

Ching teaches that antibodies to the extracellular domain of the EGF receptor inhibited growth in a dose-dependent manner. Ching does not disclose specific antibodies, nor does Ching disclose the characteristics of antibodies that inhibit growth that would be useful for

treating prostate cancer. Such *in vitro* experiments provide no bases for predicting an *in vivo* effect (absent the teaching of the invention), or even a comparison of relative activities. As evidenced by the discussion of Arakawa and Greene above, alternative mechanisms such as ADCC and enhanced antigen presentation can result in tumor growth inhibition.

The data presented in the specification of the claimed invention support that 2C4 blocks EGF, TGF-alpha, and heregulin-mediated activation of MAP kinase to a greater extent than 4D5 (Example 4, page 50). Example 1 (page 45) demonstrates that 2C4 inhibits proliferation of HER2 over-expressing cell line SK-BR-3 to a greater extent than 4D5. The superior results elicited by 2C4 are due to its biological characteristic of "blocking ligand activation" as outlined in the specification (page 13, line 37 to page 14, line 12) by *e.g.*, "preventing association with either EGFR or ErbB3" (page 50, lines 24-26). The relevant inquiry for obviousness is whether the prior art suggests the invention and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art and not in the Applicant's disclosure. *In re Vaeck*, 20 USPQ 2d 1438 (Fed. Cir. 1991). Accordingly, this rejection should be withdrawn.

The Examiner has rejected claims 1, 8, and 16 under 35 U.S.C. §103(a). The Examiner contends that the rejected claims are unpatentable over Ching, May 1995, in view of Baselga et al., Oncology, Suppl. 2, March 1997 ("Baselga I"), or Baselga et al., Journal of Clinical Oncology, Vol. 14, No. 3, pages 737-744, March 1996 ("Baselga II"). The Examiner contends that Baselga I and Baselga II teach a method of treating a human patient whose

diagnosis includes the overexpression of ErbB2 receptor by administering an effective amount of anti-ErbB2 antibody which binds the extracellular domain. As discussed above, the Examiner contends that Ching teaches a method of treating prostate cancer by administering an antibody which binds ErbB2 and blocks activation of an ErbB receptor. As Murphy is relevant, if at all, to claim 16, and this claim has been cancelled, Applicants address the rejection of claims 1 and 8.

Applicants respectfully traverse this rejection and reconsideration is respectfully requested.

Baselga I discusses the use of anti-HER2 antibodies to treat breast malignancies. Baselga I discloses that 4D5 is a potent antibody for this purpose. Baselga I also discloses that recombinant humanized 4D5 (Herceptin®) is more potent than murine 4D5 as it is "much more efficient in supporting antibody-dependent cellular cytotoxicity" (page 46, col 1). Baselga I does not disclose that humanized or murine 4D5 HER2 blocks ligand-mediated activation to a greater degree than itself, as required by the claimed invention.

Baselga II discloses results of Phase II studies with Herceptin ® in the treatment of breast cancer. On page 742, col. 1, line17-19, to col. 2, line 1-17 Baselga II discusses several possible mechanisms that could explain the observed results, including HER2 receptor down-regulation, agonistic induction of a "death-inducing" signaling pathway, and induction of ADCC. Blocking ligand-mediated activation is not specifically disclosed.

In view of the above, absent specific teaching in Ching of a comparative ability of an anti-ErbB to inhibit ligand activation, much less the relationship of such a characteristic to treating prostate cancer, and a similar lack of disclosure in Baselga I, and Baselga II, the combination of references fails to suggest the invention. As pointed out above, the relevant

inquiry for obviousness is whether the prior art suggests the invention and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. *O'Farrell*, 7 USPQ2d 1673. Both the suggestion and the reasonable expectation of success must be found in the prior art and not in the Applicant's disclosure. *Vaeck*, 20 USPQ 2d 1438. In this case, the references provide no suggestion of the invention, much less a reasonable expectation of successfully achieving the invention. Accordingly, this rejection should be withdrawn.

The Examiner has rejected claims 1-5, 8, 16, and 20 under 35 U.S.C. §103(a). The Examiner contends that the rejected claims are obvious over Greene, or Arakawa, as evidenced by Murphy, in view of Fendly et al., Cancer Research, Vol. 50, pages 1550-1558, March 1, 1990 ("Fendly"), or Shepard et al., Journal of Clinical Immunology, Vol. 11, No.9, pages 117-126, 1991 ("Shepard"). The teachings of Greene, Arakawa and Murphy have been discussed above. The Examiner contends that Fendly and Shepard teach the monoclonal antibody 2C4 selectively binds HER2, and that it would have been obvious for one of ordinary skill in the art to use the 2C4 antibodies of Fendly and Shepard to practice the methods of Greene and Arakawa. The Examiner asserts that blocking ligand activation would be an inherent characteristic of the Fendly and Shepard antibodies. To the extent that claims 16 and 20 have been cancelled, and Murphy applies if at all to these claims, Applicants address the rejection of claims 1-5 and 8.

Applicants respectfully traverse this rejection and reconsideration is respectfully requested.

Fendly teaches that monoclonal antibody 2C4 is intermediate in its ability to immunoprecipitate HER2, and that two other anti-EGFR monoclonal antibodies (5G3 and 6C5)

blocked ligand binding to EGFR (*not* to its oncogenic counterpart HER2/ErbB2). Fendly does not teach or suggest that (1) 2C4 (or any antibody) blocks ligand activation of an ErbB receptor, as recited in the claims herein, or (2) that such a property renders the antibody useful for treating prostate cancer.

Shepard teaches that the mechanism by which 2C4 inhibits growth of breast tumor cells is not understood, but that it likely is due to cross-reactivity with another receptor on the cell surface (page 120, col. 2). Shepard further explains that a "critical property" of an anti-$p185^{HER2}$ antibody with potential for therapy is its lack of cross-reactivity with other receptors (page 119, col. 2). Like Fendly, Shepard does not teach that 2C4 blocks ligand activation of an ErbB2 receptor as reacted in the claims, or that such a property renders the antibody useful for treating prostate cancer. Fendly describes production of a panel of 10 anti-$p185^{HER2}$ monoclonal antibodies, without indicating which, if any, are potentially therapeutic (Fendly does note that prior publications reported that several anti-$p185^{HER2}$ monoclonal antibodies inhibit breast cell line proliferation *in vitro*, citing, Hudziak *et al.*, Mol. Cell Biol. 1989, 9:1165-1172). Shepard promotes antibody 4D5, one of over 100 monoclonals tested, for treating p185 HER2 over-expressing tumor cells. Shepard further teaches away from using a cross-reactive antibody, like 2C4, in therapy (Shepard, pps. 119-120). These two references, taken for what they fairly teach, when combined with the primary references, lead one to employ 4D5 to treat prostate cancer. Indeed, Shepard reports that 4D5 was most effective against another cancer besides breast carcinoma, as it was also effective against an ovarian tumor line (Shepard, p. 120). No other conclusion is fairly available from this combination of references. But the claimed invention recites that the antibody block ligand activation of an ErbB receptor, *i.e.*, more effectively than

4D5, thus distinguishing the claims from the very subject matter that the references lead one of ordinary skill in the art to pursue.

Certainly there is no reasonable expectation that therapy with antibodies that bind $p185^{HER2}$, and not pursued in deference to antibody 4D5, would be effective for treating prostate cancer. The only basis for such a conclusion is in the instant invention, and clearly the rejection relies on hindsight gained from the instant disclosure to support this rejection. Such a basis for rejecting the claims is improper. The Examiner cannot rely on hindsight to arrive at a determination of obviousness. *In re Fritch*, 23 U.S.P.Q.2d 1780, 1784 (Fed. Cir. 1992). The Court of Appeals for the Federal Circuit has stated that "selective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings. There must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the Applicant's disclosure" [*Interconnect Planning Corporation v. Fed.*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985)]. *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988).

The Examiner has rejected claims 1-6, 8-9, 16, and 20 under 35 U.S.C. §102(e). Applicants presume from (1) the reasoning for this rejection and (2) the fact that Curnow is not a patent that the Examiner meant §103(a). The Examiner contends that the rejected claims are obvious over Curnow, as evidenced by Murphy, in view of Fendly, or Shepard. The teachings of Curnow, Murphy, Fendly and Shepard have been discussed above. The Examiner contends that it would have been obvious to one of ordinary skill in the art to use the 2C4 antibodies of Fendly and Shepard, in the method of Curnow, as the antibodies bind HER2 and were known to treat tumor cells over-expressing HER2. The Examiner asserts that the ligand-blocking would be an

inherent characteristic of the Fendly and Shepard antibodies.

Applicants respectfully traverse this rejection and reconsideration is respectfully requested.

As discussed above, Curnow teaches a bi-specific antibody capable of bringing a CD64-positive effector cell in contact with HER2 target cell. Logically, the best choice for such a construct would be an antibody with high affinity for HER2. From Shepard (Fig. 2 and Table I) and Fendly (Fig. 1 and Table 1) (the data in both references are the same), we see that the antibody of choice is not 2C4, or even 4D5, but rather 7F3, which has the greatest O.D. of binding in Figure 1, and has highest results for binding activity by ELISA, radioimmunoprecipitation (RID), and FACS (Table 1). Furthermore, since Shepard clearly identifies 4D5 as the best therapeutic candidate, it is clear that the criteria for activity according to Curnow do not define a useful therapeutic antibody, as claimed. In short, there is no incentive to combine these references, and the references, if combined, do not teach the claimed invention. They teach away from it, which is the paradigm of a lack of a reasonable expectation of success. Generally, when a reference teaches away from the claimed invention, the requisite teaching to establish *prima facie* obviousness is absent, thus precluding a conclusion of unpatentability. See *In re Bell*, 26 USPQ2d 1529 (Fed. Cir. 1993). The Court of Appeals for the Federal Circuit has stated:

> A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent form the path that was taken by the applicant [citation omitted].

In re Gurley, 27 F.3d 551 (Fed. Cir. 1994). Therefore, withdrawal of this rejection is respectfully requested.

The Examiner has rejected claims 1-5, 8, 16, and 20 under 35 U.S.C. §103(a). The Examiner contends that the rejected claims are unpatentable over Hudziak, as evidenced by Murphy, in view of Ching, further in view of Fendly or Shepard. The Examiner contends that it would have been obvious to use the 2C4 antibodies of Fendly and Shepard in the method of Hudziak, Murphy and Zhi.

Applicants respectfully traverse this rejection and reconsideration is respectfully requested. For the reasons advanced above, Fendly and Shepard do not supply the deficiencies of the other references. Indeed, these references lead the skilled artisan towards antibodies like 4D5 rather than antibodies like 2C4. Thus, applying the legal principles set forth above, one must conclude that the references fail to suggest the invention, and instead lead away from it, both of which preclude a determination of obviousness.

The Examiner has rejected claims 1-5, 8, 16, and 20 under 35 U.S.C. §103(a). The Examiner contends that the rejected claims are unpatentable over Ching, in view of Baselga I, or Baselga II, in view of Fendly or Shepard. The Examiner contends that it would have been obvious to one of ordinary skill in the art to use the 2C4 antibodies of Fendly and Shepard to treat cancer as disclosed in Baselga I, Baselga II and Zhi, as the antibodies were known to bind HER2.

Applicants respectfully traverse this rejection and reconsideration is respectfully requested.

For reasons extensively set forth above, Applicants assert that the references, if combined as suggested, lead one to select antibody 4D5 to treat prostate cancer. It bears noting at this point that 4D5 antibodies like Herceptin® may be useful cancer therapeutics. However, the present invention is distinct from such teachings because the antibody must block ligand activation of an ErbB receptor, which means more than 4D5. Since it is quite clear that 4D5 cannot meet this limitation, the claimed invention is unobvious. Withdrawal of this rejection is respectfully requested.

Lastly, the Examiner has rejected claims 1-5, 8, 16, and 20 under 35 U.S.C. §103(a). The Examiner contends that the rejected claims are unpatentable over Greene or Arakawa or Curnow, or Hudziak, or Zhi, or Baselga I, or Baselga II, in view of Fendly, or Shepard, all in view of Schlom, Molecular Foundations of Oncology, pages 95-134, 1991 ("Schlom"). The Examiner contends that Schlom describes the various known antibody modifications, including Fab's and that these fragments provide a therapeutic advantage of reducing the host anti-monoclonal antibody response. Thus, the Examiner alleges that it would have been obvious to use the Fab's of Schlom to practice the methods of Greene, or Arakawa or Curnow or Hudziak or Zhi or Baselga I or Baselga II or Fendly or Shephard, and one would have been motivated to do so because the Fab's reduce the host anti-antibody response.

Applicants respectfully traverse this rejection and reconsideration is respectfully requested. As pointed out above, none of the references taken alone or in combination describe using an antibody that binds an ErbB receptor and blocks ligand activation of an ErbB receptor, *i.e.*, greater than antibody 4D5, to treat prostate cancer. If the references teach anything, it is to use a 4D5

antibody to treat prostate cancer. While this may very well be a useful prostate cancer treatment modality, since 4D5 cannot be more effective than 4D5 in blocking ligand activation of an ErbB receptor, the claimed invention distinguishes over all of the references in combination (noting, for the record, that some or all of the combinations are simply improper).

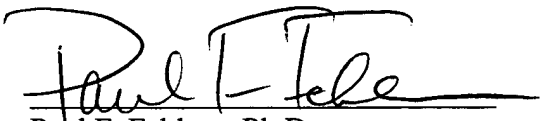
Schlom does not provide the missing teaching. The description of antibody fragments can hardly substitute for the teaching found in the specification: that an antibody having the claimed properties will be useful for treating prostate cancer. Therefore, in view of the above remarks and the legal principles of obviousness, withdrawal of this rejection is in order.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks into the file history of this application. All of the alleged grounds for unpatentability of the claims have been addressed by this response. Applicants earnestly solicit allowance of the application.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,



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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: David B. Agus; Howard I. Scher; Mark X. Sliwkowski

Serial No.: 09/602,800 Art Unit: 1642

Confirmation No.: 1759

Filed: 6/23/00 Examiner: Jennifer E. Hunt

For: TREATING PROSTATE CANCER WITH ANTI-ERBB2 ANTIBODIES

MARK-UP FOR AMENDMENT UNDER 37 C.F.R. §1.121

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

August 13, 2002

Sir:

IN THE SPECIFICATION:

On page1, line 23, to page 2, line 5:

The second member of the ErbB family, p185^{neu}, was originally identified as the product of the transforming gene form neuroblastomas of chemically treated rats. The activated form of the *neu* proto-oncogene results from a point mutation (valine to glutamic acid) in the transmembrane region

of the encoded protein. Amplification of the human homolog of *neu* is observed in breast and ovarian cancers and correlates with a poor prognosis (Slamon *et al.*, *Science*, 235:177-82 (1997); Slamon *et al.*, *Science*, 244:707-712 (1989); and U.S. Pat. No. 4,968,603). To date, no point mutation analogous to that in the *neu* proto-oncogene has been reported for human tumors. Overexpression of ErbB2 (frequently but not uniformly due to gene amplification) has also been observed in other carcinomas including carcinomas of the stomach, endometrium, salivary gland, lung, kidney, colon, thyroid, pancreas and bladder. See, among others, King *et al.*, *Science*, 229:974 (1985); Yokota *et al.*, Lancet[:], 1:765-767 (1986); Fukushig[i]e *et al.*, *Mol. Cell Biol.*, 6:955-958 (1986); G[e]uerin *et al.*, *Oncogene Res.*, 3:21-31 (1988); Cohen *et al.*, *Oncogene*, 4:81-88 (1989); Yonemura *et al.*, *Cancer Res.*, 51:1034 (1991); Borst *et al.*, *Gynecol. Oncol.*, 38:364 (1990); Weiner *et al.*, *Cancer Res.*, 50:421-425 (1990); Kern *et al.*, *Cancer Res.*, 50:5184 (1990); Park *et al.*, *Cancer Res.*, 49:6605 (1989); Zhau *et al.*, *Mol. Carcinog.*, 3:[3]254-[3]257 (1990); Aasland *et al.*, *Br. J. Cancer*, 57:358-363 (1988); Williams *et al.*, *Pathiobiology*, 59:46-52 (1991); and McCann *et al.*, *Cancer*, 65:88-92 (1990). ErbB2 may be overexpressed in prostate cancer (Gu *et al.*, *Cancer Lett.*, 99:185-189 (1996); Ross *et al.*, *Hum. Pathol.*, 28:827-833 (1997); Ross et al., *Cancer*, 79:2162-2170 (1997); and Sadasivan *et al.*, *J. Urol.*, 150:126-131 (1993)). Antibodies directed against the rat p185^{neu} and human ErbB2 protein products have been described. Drebin and his colleagues have raised antibodies against the rat *neu* gene product, p185^{neu}. See, for example, Drebin *et al.*, *Cell*, 41:695-706 (1985); Myers *et al.*, *Meth. Enzym.*, 198: 277-290 (1991); and WO94/22478. Drebin *et al.*, *Oncogene*, 2:273-277 (1988) report that mixtures of antibodies reactive with two distinct regions of p185^{neu} result in synergistic anti-tumor effects on *neu*-transformed NIH-3T3 cells implanted into nude mice. See also U.S. Patent 5,824,311, issued October 20, 1988.

On page 43, lines 5-14:

The murine monoclonal antibodies 2C4, 7F3, and 4D5 which specifically bind the extracellular domain of ErbB2 were produced as described in Fendly *et al.*, *Cancer Research*, 50:1550-1558 (1990). Briefly, NIH 3T3/HER2-3_{400} cells (expressing approximately 1 x 10^5 ErbB2 molecules/cell) produced as described in Hudziak *et al.*, *Proc. Natl. Acad. Sci (USA)*, 84:715[8]9-7163 (1987) were harvested with phosphate buffered saline (PBS) containing 25 mM EDTA and used to immunize BALB/c mice. The mice were given injections i.p. of 10^7 cells in 0.5 ml PBS on weeks 0, 2, 5, and 7. The mice with antisera that immunoprecipitated ^{32}P-labeled ErbB2 were given i.p. injections of a wheat gem agglutinin-Sepharose (WGA) purified ErbB2 membrane extract on weeks 9 and 13. This was followed by an i.v. injection of 0.1 ml of the ErbB2 preparation and the splenocytes were fused with mouse myeloma line X63-Ag8.653. Hybridoma supernatants were screened for ErbB2-binding by ELISA and radioimmunoprecipitation.

On page 54, lines 33-36, please replace with the following paragraph:

Real Time Quantitative PCR. TGF-α and HB-EGF mRNA was quantified using real time quantitative PCR or TaqMan technique as previously described (Gibson *et al.*, *Genome Research*, 6:[986-994]995-1001 (1996); and Heid *et al.*, *Genomic Research*, 6:986-994 (1996)). The sequence of the primer/probe sets used for this analysis are shown below: